REMARKS

This is in response to the final Official Action mailed March 29, 2001 in the above-referenced application and the Interview Summary provided at an Interview on April 24, 2001. The Examiner is thanked for the opportunity to discuss the case in order to clarify the issues raised in the Office Action with respect to the prior art.

Claims 1-3, 5, 6, 7, 10, 12-15, 19-35, 37, and new claim 38 are before the Examiner. Applicants note with appreciation the indication by the Examiner that Claims 10, 20 and 37 are allowed. Claim 11 has been cancelled without prejudice.

New claim 38 recites one advantageous embodiment of the invention, in which the bioactive artificial sintered composition of the invention includes silicon stabilizing entities. This claim is presented as a substitute for previously cancelled claim 7. This claim does not raise new issues for the Examiner, nor require a new search, because this aspect of the invention has been before the Examiner throughout prosecution. See, for example, pending claim 5.

Claims 1, 5, 6, 13, 19, 24, 25 and 27 are amended. The amendments made to the claims highlight certain features thereof and better distinguish the claimed invention from that of the cited prior art. These amendments also do not raise new issues for consideration by the Examiner nor require a new search.

In particular, as discussed during the interview, independent claims 1, 13, 19, 24, and 27 are amended to clarify various aspects of the invention, namely, that the stabilizing entities are substantially uniformly distributed throughout the calcium phosphate phases; and that the insolubilized tricalcium phosphate is insoluble in physiological fluids. The Applicants have maintained throughout the prosecution of the application that the presently claimed composition is uniformly doped with stabilizing entities, leading to a uniformly stabilized tricalcium phosphate which is insoluble in physiological fluids. The claim amendments are presented to better point out this characteristic feature and to do so consistently throughout the claims. Applicants respectfully submit these amendments also do not raise new issues or require a new search and accordingly request entry of the same.

Claims 1, 5 and 6 are also amended in view of the discussion during the Interview. During the Interview, one of the co-inventors Tim Smith explained to the Examiner that the

presently claimed composition is an isolated and uniformly stabilized tricalcium phosphate that has unique properties. As such, claims 1, 5, and 6 have been amended to focus on the composition per se without relying on any processing steps, particularly since such steps are not required to distinguish the novel composition over the art. Further, the application includes separate process claims so that it was thought that the composition per se claims should be separate from any process type claims.

Claim 25 has been amended to delete the term "surface" since Figure 14 as recited in this claims shows both surface and internal morphology.

The issues raised in the Official Action and during the Examiner Interview are addressed below.

Claim Rejections under 35 USC § 102

Claims 1-3, 5, 6, 11-15, 21-23, 31 and 33-35 are rejected under 35 USC §§102(a) or (b) as being anticipated by Davies (WO 94/26872). Applicants respectfully disagree with the Examiner with respect to both the §§102(a) and/or (b) rejection and submit that the Davies reference does not anticipate the noted claims.

The Examiner asserts that Davies discloses a sintered hydroxyapatite film in a manner similar to the present invention due to the silica of quartz permeating into the sol during sintering. In this regard, the Davies reference is directed to a calcium phosphate based thin film for culturing bone cells thereon. The Davies publication does not specify the make up of the thin film therein, other than to note that the thin film comprises both calcium hydroxyapatite and tricalcium phosphate in different ratios. Indeed, as the Office acknowledges, Davies is completely silent as to the provision of stabilized calcium phosphate phases.

As was discussed with the Examiner during the Interview, the Davies thin film is made up of a complex mixture of stratified calcium phosphate phases, some of which may be partially stabilized to varying degrees. This is discussed in the present application on page 17 with reference to Figures 6(a)-(c). Figure 6(a) shows the Davies thin film in cross section with an EDX analysis performed at various locations throughout the thin film. The regions shown are the interface of the film and the substrate, the intermediate region above the interface, and the top

of the film. As seen in these analysis, the Davies thin film has varying compositions throughout and thus is a complex mixture of several different calcium phosphate phases. The amount of silicon present in the various regions also differs significantly. See Figures (c)(i) – (iii), which illustrate the different amounts of silicon distributed throughout the Davies product.

Thus Davies illustrates a complex mixture of various calcium phosphate phases, in which silicon is not uniformly distributed. Indeed, data in the present application demonstrate that different regions of the Davies material include different amounts of silicon. Davies did not realize the make up of the thin film and certainly did not teach the benefit of any particular stabilized portion of the thin film that existed. Further, Davies did not teach or suggest isolating a particular uniformly stabilized tricalcium phosphate phase useful for a variety of applications.

In contrast, the claimed invention is directed to a tricalcium phosphate composition in which stabilizing entities, such as silicon, are uniformly distributed. As discussed during the interview, the composition is prepared by uniformly distributing, or doping, a hydroxyapatite substance with stabilizing entities. For example, in one aspect of the invention the hydroxyapatite is doped with stabilizing entities provided in solution so that the stabilizing entities are uniformly distributed throughout the hydroxyapatite before sintering. The uniformly doped hydroxyapatite is then sintered to convert it into tricalcium phosphate. Because the starting material is uniformly doped with stabilizing entities, the stabilizing entities are also uniformly distributed throughout the resultant tricalcium phosphate composition. This in turn provides a uniformly stabilized composition.

Surprisingly the Applicants have found that the claimed compositions of the present application support osteoblastic bone growth over and throughout structures made of the composition. The materials also promote natural controlled extracellular resorption of the composition by osteoclasts, while avoiding non-specific chemical and/or cellular dissolution and/or degradation, in a process resembling that of normal bone turnover. See pages 10, 19 and 22-23 of the present application. The Applicants were the first to develop and characterize a stabilized composition which behaves similar to natural bone, and which in fact integrates with the natural bone over time so that an implant formed of the composition is progressively replaced by natural bone.

Not only does the Davies thin film as provided on a quartz substrate differ compositionally from the claimed invention, in that the mixture of calcium phosphate phases which constitute the thin film of Davies are not uniformly stabilized. In Davies, the mixture of phases is entirely dependent on the provision of a substrate on which the thin film is made and always supported thereon. Davies always refers to the "substrate" for providing support for the thin film and which can allow for certain analytical assessment of the film after the culture of the cells. Davies nowhere teaches or suggests the chemical effect a quartz substrate would have, if any, on the thin film. Its sole contemplated use is to provide a suitable physical substrate that could be sintered and could be used in analytical testing. This is also further supported by the fact that Davies teaches the use of other materials such as metals, polymers or ceramics as a support. Davies further does not teach or suggest that its thin film supported on a substrate could be used in other forms or applications, such as three dimensional structures or implants.

In summary, the claimed invention is not inherent and not anticipated by the Davies reference. Davies does not teach anything more than a thin analytical film comprising a stratified mixture of partially stabilized calcium phosphate phases, which are formed by the inadvertent addition of silicon from the quartz substrate in a non-uniform manner. Davies does not teach the chemical function of quartz in the compositions. Further, the Davies thin film, which is supported by a substrate, cannot be used or made into three-dimensional structures or implants.

In contrast, the presently claimed invention is an entirely different composition from that taught by Davies, both structurally and with respect to its characteristic features. The presently claimed isolated uniformly stabilized tricalcium phosphate composition is not taught or suggested by Davies. This is a different composition to that taught by Davies. The claimed composition can be used in a variety of forms, including as three-dimensional structures or implants. The claimed process is even further removed from Davies, which nowhere teaches or suggests uniformly doping a hydroxyapatite substance with stabilizing entities prior to sintering. Accordingly Applicants request withdrawal of this rejection.

Claims 1-3, 12-14, 19, 22, 23, 31 and 34 are also rejected under 35 USC § 102(b) as being anticipated by Kasuga et al (U.S. 5,232,878). Claims 1-3, 5, 6, 11-14, 21, 23, 24 and 31-

34 are also rejected under 35 USC § 102(b) as being anticipated by Kijima et al (U.S. 4,983,182). The cancellation of claim 11 renders the rejection of this claim *moot*. Again, the Applicants respectfully disagree with the Examiner.

The present invention as noted in independent claims 1, 13, 19 is directed to a bioactive composition which supports bone cell activity thereon. During the Interview with the Examiner the Examiner had suggested that the term "bioactive" as recited in the claims referred to "biocompatible" as taught by these cited references. The Examiner explained that if the term "bioactive" had a clear meaning in the claim and was supported by the description to in fact be different from "biocompatible" then the Examiner would consider this to bear weight with respect to patentably distinguishing the present claims from the cited art.

The term "bioactive" is explicitly defined in the present specification at page 10 and also further described on pages 19 and 22-23. In the description "bioactive" is defined as "the ability to support osteoblastic bone growth over and throughout structures substantially or exclusively made of the presently claimed composition and simultaneously promote natural controlled extracellular resorption of the composition by osteoclasts, while avoiding non-specific chemical and/or cellular dissolution and/or degradation, in a process resembling that of normal bone turnover". Thus the presently claimed composition is useful for applications in which "true" *in vivo* bone remodeling is desired. This is a unique feature of the presently claimed composition that is not taught or suggested by Kasuga or Kijima.

Kasuga is directed to a process for producing an inorganic biomaterial which has a good strength and biocompatibility such that it can be used as a dental implant or an artificial bone implant. "Biocompatibility" refers to the fact that the material as produced can be used *in vivo* as an implant and generate bone bonding. This is clearly not the same as "bioactive" as is recited in the present claims and discussed above. The implant of Kasuga is an inhomogeneous physical dispersion of crystallized glass or calcium phosphate within a skeleton of zirconia, which provides for increased mechanical properties. The fact that Kasuga is directed to a "glass" structurally identifies the material as being different to that presently claimed. It is only in the later steps of Kasuga's process that the glass is heated to form a crystallized powder which is then mixed with stabilized zirconia or alumina wherein "stabilization" is meant that the zirconia

is prepared to attain high strength and high toughness with respect to stress-induced transformation (column 6, lines 38-44) such that it can be used as a biomaterial for artificial bones and dental implants. This strength orientated stabilization in no way resembles the present biological stabilization of calcium phosphate phases.

Kijima is directed to an interfacial layer on the surface of a zirconia implant which allows for chemical bonding of the implant to vital tissue. The Kijima reference refers to "biologically active" which is directed to ability of the implant to be bonded to bone. This is not the same as "bioactive" as is recited in the present claims as is discussed *supra*. Again, as with Kasuga, "stabilized zirconia" refers to enhanced mechanical stability and strength and not to stabilization leading to insolubility in physiological fluids and "bioactivity" leading to natural bone remodeling.

Neither the Kasuga or the Kijima taught materials support "bone cell activity" leading to *in vivo* bone remodeling as the case in the presently claimed composition. The Applicants were the first to develop and characterize a stabilized composition which behaves similar to natural bone. This has numerous advantages over the conventional types of implants as taught by these cited references. Most notably, the presently claimed composition as provided as an implant integrates with the natural bone over time the implant is remodeled by bone cell activity such that the implant is progressively replaced by natural bone.

Furthermore, neither Kasuga or Kijima teach or suggest a uniformly stabilized tricalcium phosphate composition which is also bioactive as discussed above. As neither of these references teach each and every element of the claim they cannot anticipate the noted claims.

Claim Rejections under 35 USC §103

Claims 24-30 and 32 are also rejected under 35 USC § 103(a) as being obvious in view of the teachings of Davies, cited above. For the reasons as provided *supra*, Applicants submit that the claimed invention is also not rendered obvious by the teachings of Davies. The presently claimed invention is a different composition having a different structure and different properties. Davies does not teach or suggest isolating or uniformly stabilizing any of the calcium phosphate phases developed in the thin film by uniform doping with exogenously added stabilizing entities

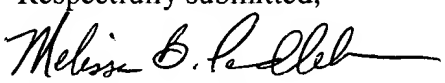
to obtain an isolated uniformly stabilized tricalcium phosphate. For these reasons the teachings of Davies do not render the noted claims obvious.

Conclusions

In summary, Applicants respectfully submit that the claimed invention is both novel and nonobvious and accordingly request withdrawal of the all rejections under 35 USC §§ 102(a) or (b) and USC § 103(a).

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,



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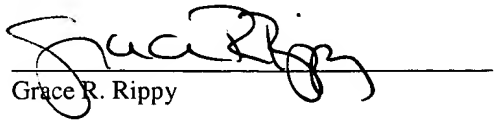

Grace R. Rippy

Version with Markings to Show Changes Made:

1. (Twice amended) A bioactive artificial sintered composition for [providing a morphology capable of] consistently supporting bone cell activity, said composition comprising substantially uniformly stabilized calcium phosphate [phases developed by the conversion of a hydroxyapatite substance doped with stabilizing entities at sintering temperatures into insolubilized and stabilized tricalcium phosphate] having stabilizing entities distributed substantially uniformly throughout, wherein said uniformly stabilized tricalcium phosphate is insoluble in physiological fluids.

5. (Twice amended) A composition as claimed in claim 3, wherein said [hydroxyapatite substance before sintering is doped with] stabilizing entities are selected from the group consisting of silicon entities, aluminum entities, zirconium entities, barium entities, titanium entities, germanium entities, chromium entities, vanadium entities, niobium entities, boron entities and mixtures thereof.

6. (Amended) A composition as claimed in claim 5, wherein said stabilizing entities are [added] provided in solution [to the hydroxyapatite substance before sintering].

13. (Twice amended) A process for stabilizing an artificial sintered composition of calcium phosphate phases having a morphology suitable for supporting bone cell activity, said process comprising substantially uniformly doping a hydroxyapatite substance with stabilizing entities and sintering said substantially uniformly doped hydroxyapatite substance; wherein sintering converts said substantially uniformly doped hydroxyapatite substance into primarily uniformly stabilized alpha tricalcium phosphate which is insoluble in physiological fluids and said stabilizing entities stabilize [and insolubilize] the formed alpha tricalcium phosphate within the phosphate phases.

19. (Amended) A process for stabilizing an artificial sintered composition of calcium phosphate phases having a morphology suitable for supporting bone cell activity thereon, said process comprising converting a hydroxyapatite substance into primarily uniformly stabilized alpha tricalcium phosphate by sintering, wherein silicon entities are [added] provided in solution

to the hydroxyapatite substance before sintering which uniformly stabilize [and insolubilize] the formed alpha tricalcium phosphate within the phosphate phases and wherein said uniformly stabilized alpha tricalcium phosphate is insoluble in physiological fluids.

24. (Amended) A sintered artificial microporous polycrystalline structure for supporting bone cell activity, said structure comprising sintered substantially uniformly stabilized calcium phosphate phases having a globular surface morphology of loosely interconnected rounded granules with interconnected micropores in said structure, wherein said substantially uniformly stabilized calcium phosphate phases are developed by the conversion of a hydroxyapatite substance substantially uniformly doped with [added] stabilizing entities at sintering temperatures into [insolubilized and] stabilized tricalcium phosphate phases, wherein said substantially uniformly stabilized alpha tricalcium phosphate is insoluble in physiological fluids.

25. (Twice amended) A polycrystalline structure of claim 24, wherein said structure has said globular [surface] morphology of Figure 14.

27. (Amended) An implantable calcified bone matrix comprising:

a) a structure for supporting said matrix;

b) a layer of substantially uniformly stabilized calcium phosphate phases developed by the conversion of a hydroxyapatite substance substantially uniformly doped with [in the presence of] stabilizing entities at sintering temperatures into substantially uniformly stabilized tricalcium phosphate where said stabilizing entities insolubilize and stabilize the calcium phosphate phases;

c) a boundary layer deposited by osteoblasts cultured on said layer of stabilized calcium phosphate phases; and

d) a mineralizing collagenous matrix secreted by such cultured osteoblasts.